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JC02 Rec'd PCT/PTO 28 MAR 2002

FORM PTO-1390 (REV. 12-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER
PAT 457W-2

U.S. APPLICATION NO. (If known, see 37 CFR 1.5
10/089220

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/CA00/01139	September 29, 2000	September 30, 1999

TITLE OF INVENTION
TRAVERSE SHEAR MODE PIEZOELECTRIC CHEMICAL SENSOR

APPLICANT(S) FOR DO/EO/US
Michael Thompson et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [ ] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: PCT/IB/308

JC13 Rec'd PCT/PTO 28 MAR 2002

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/089220	PCT/CA00/01139	PAT 457W-2

	CALCULATIONS	PTO USE ONLY
21. [X] The following fees are submitted: **BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):** Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO .... **$1040.00** International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO .... **$890.00** International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO .... **$740.00** International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) .... **$710.00** International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	- 20 =		x **$18.00**	$	
Independent claims	- 3 =		x **$84.00**	$	
MULTIPLE DEPENDENT CLAIM(S) (if applicable) 2			+ **$280.00**	$ 560.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1.580.00	
[X] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. / +				$ 790.00	
SUBTOTAL =				$ 790.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 790.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 790.00	
				Amount to be refunded:	$
				charged:	$

a. [ ] A check in the amount of $ ______________ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 501593 in the amount of $ 790.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 501593. A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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26123
PATENT TRADEMARK OFFICE

Kathleen Marsman
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48,121
REGISTRATION NUMBER

10/089220
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TRAVERSE SHEAR MODE PIEZOELECTRIC CHEMICAL SENSOR

Field of the Invention

This invention relates to a process of detecting specific molecules in a liquid (the analyte) with receiving molecules, (the receptors) which are attached to the surface of a thickness shear mode acoustic sensor (TSM). Acoustic energy generated in the sensor is transferred to and from the fluid depending on the surface coupling behaviour. The coupling is altered when the analyte binds to the receptor producing easily measured changes in the electrical characteristics of the sensor.

The invention further relates to the application of the measurement of the coupling effects to the sensing of biomolecules, and other molecules of biological significance such as drugs, in general. For example, the receptor may be a protein, a single oligonucleotide strand, DNA or RNA and the analyte a protein, drug or complementary strands of DNA or RNA. The interaction between the analyte and the sensor bound receptor can be identified through a quantitative TSM response. Other measurement scenarios are possible through the detection of changes in the acoustic coupling between the sensor surface and the surrounding liquid.

Background of the Invention

A TSM sensor is a device which generates mechanical vibrations from an electrical signal and uses these vibrations to detect and/or quantify particular chemical or biochemical substances present in a medium surrounding the sensor (the analyte). Acoustic energy is stored and dissipated both in the device itself, and through interfacial coupling, in a surrounding liquid medium. By coating the sensor with one or more layers of a substance which interacts with the analyte, the energy storage and transfer processes change when the interaction occurs. This changes the acoustic resonance of the sensor, which can be observed by measuring the electrical impedance of the sensor. The

applicants have published several papers in this field and they are listed as follows:

1) F. Ferrante, A.L. Kipling and M.Thompson, "Molecular Slip At The Solid-Liquid Interface Of An Acoustic Wave Sensor", *J. Appl. Phys.* 76(6):3448-3462, 1994;

2) G.L. Hayward and M. Thompson, "A Transverse Shear Model Of A Piezoelectric Chemical Sensor", *Amer. Inst. Physics* 83(40:2194-2201, 1998;

3) Cavic B.A. et al., "Acoustic Waves And The Real-Time Study Of Biochemical Macromolecules At The Liquid/Solid Interface", *Faraday Discuss.* 107:159-176, 1997;

4) H. Su and M. Thompson, "Rheological And Interfacial Properties Of Nucleic Acid Films Studies By Thickness-Shear Mode Sensor And Network Analysis", *Can. J. Chem.* 74:344-358, 1996.

There are several mechanisms whereby a TSM sensor responds to chemical change on its surface when it is immersed in a liquid. Surface mass deposition occurs when the analyte binds to the receptor on the sensor surface. This increases the storage of acoustic energy through the inertia of the added mass. Acoustic energy may also be stored through the elastic deformation of a coating on the surface. The elasticity of the coating may also change when the analyte binds to the receptor coating. These energy storage modes determine the resonant characteristics of the sensor which can easily be measured electrically. These processes are well known. Examples of piezoelectric sensors are described, for example in U.S. Patents 5,374,521 and 5,658,732.

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Viscous loading occurs when acoustic energy is transferred to the liquid. Some of the acoustic energy is stored by the inertia of the fluid moving with the sensor surface and can be transferred back to the sensor, but acoustic energy is also dissipated by internal friction within the fluid. The viscous loading effect is also well known, however in the current use of this effect, the transfer of acoustic energy at the surface is considered to be perfect, that is, there is no slip between the sensor surface and the adjacent fluid molecules.

The current practice is based on the well known Butterworth - van Dyke model of a piezoelectric resonator which consists of a resistor, inductor and capacitor in series, all in parallel with another capacitor. The series arm of this network is called the motional arm. Further details of this model and the calculation of the following parameters may be found in the above paper entitled "Rheological and Interfacial Properties of Nucleic Acid Films Studies by Thickness-Shear Mode Sensor and Network Analysis".

Motional Inductance

The motional inductance, L_M, represents the inertial energy stored by the sensor. It depends on the mass of the TSM sensor as well as the mass of material (the analyte) added to the surface. Since liquid coupled to the surface can store and return acoustic energy, L_M is also dependent on the viscosity of the liquid.

Motional Resistance

The motional resistance, R_M, is intrinsically related to the energy dissipated by the sensor.

Accordingly, any imposition of material (or loss of material) that has a viscous property or changes in the viscosity of the liquid will result in a change in the energy dissipation and hence R_M.

Motional Capacitance

The motional capacitance, C_M, represents the elastic energy stored by the sensor. The absorption or chemical binding of the analyte to the coating can have a large effect on the viscoelastic properties of the coating. Depending on the thickness, an added (or removed) layer of material may change the elasticity of the sensor and thus affect C_M. Although most fluids are considered to be viscous, at the high frequencies used in piezoelectric quartz sensors, the liquid may also have elastic properties.

Static Capacitance

The static capacitance C_O represents the dielectric constant of the quartz, but includes that of the medium through the electric field. Charge interactions between the analyte and the sensor coating will affect this value.

Summary of the Invention

According to an aspect of the invention, there is provided a process for sensing biological or chemical changes in molecular structural shape or mass of molecules attached to the surface of a transverse shear piezoelectric oscillating molecular sensing device driven by a network analyzer, said process comprising:

i) exciting said sensor device at a series of predetermined frequencies;

ii) collecting data to determine values for the predetermined parameters of series resonance frequency shift (fS), motional resistance (RM), motional inductance (LM), motional capacitance (CM), electrostatic capacitance (Co) and boundary layer slip parameter (α); and

iii) determining relative changes in said measured parameters to detect thereby any changes in molecular structural shape or mass at sensing device surface.

In accordance with another aspect of the invention there is provided a method of determining the efficiency of acoustic coupling between a sensor and the surrounding fluid, said method comprising:

a) applying an electrical signal of known frequency and voltage to the sensor;

b) measuring the current through the sensor to determine the impedance at the known frequency;

c) repeating steps a) and b) over a range of frequencies to generate a set of impedance data; and

d) fitting the measured impedance data to determine an α parameter which represents coupling strength.

Detailed Description of the Preferred Embodiments

This invention is based on the measurement of phenomena based on imperfect acoustic coupling between the sensor surface and the liquid. The nature of this coupling determines the strength of the viscous loading and elastic effects depending on such parameters as the surface free energy and the molecular conformation of the sensor coating. These molecular parameters are very sensitive to chemical changes at the surface and therefore acoustic coupling provides a novel sensing mechanism.

The impedance measurements are carried out by applying an electrical signal of known frequency and voltage to the sensor and measuring the current through the sensor. Through Ohm's law, this provides the impedance at the known frequency. By performing this measurement over a range of frequencies, a set of data is generated. The above described, specifically selected parameters of L_M, R_M, C_M and C_O have been found to be the determining parameters for indicating a mass or conformation change at the TSM surface. Hence these parameters are fitted to the data.

While the Butterworth - van Dyke model provides useful information, it is an electrical analogy which presents the information unclearly. An alternate model of the TSM sensor is based on a solution of the equations of motion and electric fields. With this second model as set out in the aforementioned paper entitled "Molecular Slip At The Solid-Liquid Interface Of An Acoustic Wave Sensor" and "A Transverse Shear Model Of A Piezoelectric Chemical Sensor", the deposited mass and the coupling may be determined directly by fitting the

electrical impedance data obtained as above. The coupling is represented by a slip parameter, α, which arises from a slip boundary condition used in solving the set of equations. The common approach is to assume perfect coupling and to set $\alpha = 1$. In this invention, α is taken to be a complex number which is determined by fitting the measured impedance data.

The sensing process is understood to be occurring at the interface between the solid device and the liquid medium. Ligands for biological macromolecules include small molecules, ions, proteins, peptides, and strands of both DNA and RNA. The interaction of these entities with the biological molecules attached to the sensor will cause an alteration of the physical properties of the film resulting, in turn, in changes in the measured parameters. These changes will very clearly result from a combination of some or all of the above response mechanisms particular for each chemical situation. In this regard, the dimensions of the newly bound ligand is an important consideration.

The signaling species coated onto the acoustic biosensor are proteins (antibodies, enzymes, hormones, molecular receptors, etc.) and nucleic acids oligonucleotides, DNA and RNA) attached to the device surface. These molecules exist in a highly hydrated form which can be considered to constitute very viscous gels.

The effect of viscous loading is the result of acoustic energy transfer to and from the surrounding medium. This in turn depends on the nature of the contact between the surface and the medium. The contact is controlled by such chemical properties as hydrogen bonding, dispersion interactions and interfacial charge. The process can be viewed as a drag existing between the surface coating and the liquid. α represents the coupling strength but also contains phase shift information. This provides additional information regarding relative mass of liquid molecules compared to those of the sensor surface and when correlated with the selected Butterworth – van Dyke model provide a determination on what is happening at the TSM surface, namely, mass and/or molecular structural shift or change in conformation.

Example

The human immunodeficiency virus type I (HIV-I) is strongly regulated at the transcriptional level by the interaction of an 86-amino acid protein, Tat, with the trans activation responsive element at the 5' -end of the viral messenger RNA transcript (TAR). The TAR-Tat system is an important target for drug discovery research because the binding of the regulatory protein to TAR can be blocked by small molecules.

In this application we compute the slip parameter α , for the binding of Tat-derived peptides to TAR immobilized on a sensor surface. The TAR RNA is synthesized, with a biotin moiety at the 5' -end, on a DNA synthesizer by standard phosphoramidite chemistry. The acoustic wave sensor is incorporated into a flow-through configuration and electrically connected to an acoustic network analyzer. A dispersion of 100-500 μl of the reagent neutravidin is injected into the apparatus and the protein adsorbs to the gold electrode surface of the acoustic wave sensor. A dispersion of biotinylated TAR- RNA (100-500 μl) is introduced into the system where the formation of the biotin-avidin complex results in attachment of TAR to the sensor surface. Various Tat-derived peptides are then introduced into the flow-trough system. In this particular application the following peptides are specified: tat_{12}, tat_{20}, and tat_{30} where the subscript refers to the number of amino acids in the peptide. Dispersions of peptide (100-500 μl) are injected into the system. On binding of peptide to TAR in real time transient responses in the aforementioned parameters are obtained. The computed $\propto$ parameter for the various responses, which distinguishes the nature on binding, are as follows:

Tat_{12} baseline 1.978 @20.85 degrees
signal 1.964 @ 20.97 degrees

Tat_{20} baseline 1.985 @21.42 degrees
signal 1.926@ 18.15 degrees

Tat_{30} baseline 1.982 @ 22.61 degrees
signal 1.994 @ 23.03 degrees

Tat_{12} displays a small decrease in slip magnitude with an increase in phase, whereas tat_{20} shows large decreases in magnitude and phase. Tat_{30} depicts smaller increase in magnitude and phase.

Although preferred embodiments of the invention have been described herein in detail, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims.

CLAIMS:

1. A process for sensing a change in molecular structural shape of a molecule attached to the surface of a transverse shear piezoelectric sensing device driven by a network analyser, said process comprising:

i) exciting said sensing device at a series of predetermined frequencies;

ii) measuring electrical impedance of the sensing device at the predetermined frequencies by determining the overall parameters of series resonant frequency (Fs), motional resistance (Rm), motional inductance (Lm), motional capacitance (Cm) and static capacitance (Co); and

iii) determining relative changes in electrical impedence over said series of predetermined frequencies indicative of a change in molecular structural shape of a molecule attached to the surface.

2. The process according to claim 1 wherein the step of determining relative changes in electrical impedence comprises the steps of:

a) determining the boundary layer slip parameter (α) from the overall parameters;

b) determining relative changes in the boundary layer slip parameter (α) to detect changes in energy coupling indicative of changes in the molecular structural shape of a molecule attached to the surface; and

c) correlating said changes in α with a calibrated set of data to determine the molecular structural shape of a molecule attached to the surface.

3. The process according to claim 1 or 2 wherein a change in the boundary layer slip parameter (α) and an essentially zero change in the series resonant frequency (Fs) indicates a change in the molecular structural shape of a molecule attached to the surface and essentially zero change in mass.

4. The process according to claims 1 and 2 wherein changes in molecular structural shape are generated by an interaction between a molecule attached to the surface of the sensing device and an entity in a surrounding liquid medium.

5. The process according to claim 4 wherein said molecule is selected from the group consisting of proteins and nucleic acids.

6. The process according to claim 5 wherein said proteins are selected from the group consisting of antibodies, enzymes, molecular receptors, receptor ligands and polypeptides.

7. The process according to claim 5 wherein said nucleic acids are selected from the group consisting of DNA, RNA and oligonucleotides.

8. The process according to claim 4 wherein said entities in said surrounding liquid medium are selected from the group consisting of proteins and nucleic acids.

9. The process according to claim 8 wherein said proteins are selected from the group consisting of antibodies, enzymes, molecular receptors, receptor ligands and polypeptides.

10. The process according to claim 8 wherein said nucleic acids are selected from the group consisting of DNA, RNA and oligonucleotides.

11. A process for detecting a change in conformation of a molecule attached to the surface of a transverse shear piezoelectric sensor, said change in conformation being imposed by interaction of said molecule with an entity in a fluid; said process comprising the steps of:

a) contacting the molecule with a fluid suspected to contain an entity capable of changing the conformation of the molecule;

b) exciting the sensor at a series of predetermined frequencies;

c) measuring electrical impedance of the sensor at the predetermined frequencies by determining the overall parameters of series resonant frequency (Fs), motional resistance (Rm), motional inductance (Lm), motional capacitance (Cm) and static capacitance (Co);

d) determining the boundary layer slip parameter (α) from the electrical impedance determined from the overall parameters;

e) determining relative changes in the boundary layer slip parameter (α) to detect changes in energy coupling indicative of a change in the conformation of the molecule;

f) correlating changes in the boundary layer slip parameter (α) with data obtained using calibrated quantities of the entity in the fluid; and

g) determining a change in conformation of the molecule attributable to interaction with the entity in the fluid.

12. The process of claim 11 wherein a change in the conformation of a molecule comprises a change in mass or a change in shape.

13. The process of claim 11 wherein said fluid flows through a chamber to contact the molecule bound to the sensor, and wherein step f) comprises correlating the boundary layer slip parameter (α) for:

(i) a baseline value of α for fluid without said entity; and

(ii) a test value of α for fluid containing said entity.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRAVERSE SHEAR MODE PIEZOELECTRIC CHEMICAL SENSOR

(57) Abstract: The present invention relates to a process for sensing biological or chemical changes in molecular structural shape or mass of molecules attached to the surface of a transverse shear piezoelectric oscillating molecular sensing device driven by a network analyzer. The process comprises the steps of i) exciting the sensor device at a series of predetermined frequencies, ii) collecting data to determine values for the predetermined parameters of series resonance frequency shift (fS), motional resistance (RM), motional inductance (LM), motional capacitance (CM), electrostatic capacitance (Co) and boundary layer slip parameter (α); and iii) determining relative changes in the measured parameters to detect thereby any changes in molecular structural shape or mass at sensing device surface.

WO 01/23892 A1

Attorney Docket #: PAT 457W-2

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are stated below next to my name.

I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Title of Invention

TRAVERSE SHEAR MODE PIEZOELECTRIC CHEMICAL SENSOR

the specification of which is attached hereto.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed:

Prior Foreign/PCT Application(s)

Country/Office	Application No.	Date of Filing	Priority Claimed
International	PCT/CA00/01139	Sept. 29, 2000	☒ YES NO ☐
			☐ YES NO ☐

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Provisional Application Number	Date of Filing
60/156,714	September 30, 1999

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first

became available between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. Applications or PCT International Applications Designating the U.S. for Benefit under 35 U.S.C. §120

Application Serial No.	Date of Filing	Status (check one)		
		Patented	Pending	Abandoned
		□	□	□
		□	□	□

POWER OF ATTORNEY

I hereby appoint the practitioners at Customer No. 26123, as my attorneys or agents with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Address all correspondence to Customer No. 26123.

Address all telephone calls to Kathleen E. Marsman, Ph. D. (613) 237-5160 (telefax: 613-787-3558).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

1. Full name of sole or first inventor

Michael — Thompson

(Given Name) *(Middle Initial or Name)* *(Family or Last Name)*

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Inventor's signature: [signature]

Date: Aug 1, 2002

Country of Citizenship: Canada

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2. **Full name of second inventor**

Gordon	L.	Hayward
(Given Name)	*(Middle Initial or Name)*	*(Family or Last Name)*

2-0

Inventor's signature: Gordon Hayward

Date: AUGUST 13 2002

Country of Citizenship: Canada

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